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Naloxone reduces the neurochemical and behavioral effects of amphetamine but not those of cocaine

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Abstract

The specific opioid receptor antagonist naloxone modifies the effects of amphetamine in a wide variety of behavioral paradigms. Naloxone also attenuates the amphetamine-induced increase in extracellular dopamine in the brain of rats. Therefore, these experiments were designed to replicate the neurochemical and behavioral interactions between naloxone and amphetamine, and to extend these observations to interactions between naloxone and cocaine. Microdialysis was performed on adult male rats of Sprague-Dawley descent. Rats were pretreated with a subcutaneous injection of 5.0 mg/kg naloxone or vehicle, which was followed 30 min later by cumulative doses of subcutaneous *d*-amphetamine (0.0, 0.1, 0.4, 1.6, 6.4 mg/kg) or intraperitoneal cocaine (0, 3, 10, 30, 56 mg/kg) at 30 min intervals. The microdialysis probes were perfused at a flow rate of 0.6 μl/min with artificial cerebrospinal fluid. Dialysate samples were collected every 10 min from either the nucleus accumbens or striatum and analyzed for dopamine content by high-performance liquid chromatography (HPLC). Locomotor activity (photobeam breaks) was monitored simultaneously with the collection of dialysate samples. Amphetamine and cocaine dose-dependently increased extracellular dopamine in both the nucleus accumbens and striatum. Naloxone pretreatment significantly reduced the amphetamine-induced increase in extracellular dopamine in both brain regions and also attenuated the increase in locomotor activity elicited by amphetamine. Naloxone pretreatment had no effect, however, on the cocaine-induced increase in extracellular dopamine or locomotor activity. These findings suggest that endogenous opioid systems play a role in mediating the neurochemical and behavioral effects of amphetamine, but not those of cocaine.

Keywords: Amphetamine; Cocaine; Locomotor activity; Microdialysis, in vivo; Opioid receptor antagonist; Dopamine; Striatum; Nucleus accumbens

1. Introduction

In the past decade, much anatomical, electrophysiological, biochemical, and behavioral evidence has accumulated to support the hypothesis that an interrelationship exists between opioidergic and dopaminergic systems in the central nervous system. For example, opioid and dopamine neurons coexist in brain areas, such as the ventral tegmental area and substantia nigra (Johnson et al., 1980; Moore and Bloom, 1978), and opioid receptors exist on dopamine neurons (Llorens-Cortes et al., 1979; Pollard et al., 1977). Morphine administered directly into the ventral tegmental area causes an excitation of dopamine neurons (Gysling and Wang, 1983; Leone et al., 1991; Matthews and German, 1984). Furthermore, agonists specific for the opioid receptor subtypes, when given either systemically or intracerebrally, alter extracellular concentrations of dopamine in both the nucleus accumbens and striatum (Di Chiara and Imperato, 1988a,b). For example, μ- and δ-opioid receptor agonists increase extracellular concentrations of dopamine, while κ-opioid receptor agonists decrease the amount of dopamine released into the synapse (Di Chiara and Imperato, 1988a; Manzanares et al., 1991; Wood and Iyengar, 1988). All of these opioid receptor-mediated effects on dopamine release can be blocked by the specific opioid receptor antagonists naloxone or naltrexone (Di Chiara and Imperato, 1988a; Spanagel et al., 1990).

Results from a wide variety of behavioral paradigms also support the idea that opioids modulate dopaminergic pathways. In intracranial self-stimulation studies,

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psychomotor stimulants, such as the indirectly acting dopamine agonist amphetamine, increase the response rate and decrease the response threshold for rewarding brain stimulation in the rat (Cassens and Mills, 1973; Schaefer and Holtzman, 1979; Stein, 1962). These effects are blocked by both haloperidol (Philips et al., 1982), a dopamine receptor antagonist, and by naloxone (Esposito et al., 1980; Holtzman, 1976). Naloxone and naltrexone also attenuate not only the amphetamine-induced increase in locomotor activity in mice, rats, guinea pigs, and squirrel monkeys (Andrews and Holtzman, 1987; Dettmar et al., 1978; Winslow and Miczek, 1988), but also the amphetamine-induced increase in operant responding maintained by food reinforcement (Harris and Snell, 1980) or shock avoidance (Holtzman, 1974). Furthermore, naloxone blocks the ability of amphetamine to establish a conditioned place preference (Trujillo et al., 1991).

The exact mechanisms by which opioid receptor antagonists decrease the action of amphetamine remain unclear. However, in a recent study, Hooks et al. (1992) demonstrated that naloxone attenuated both the amphetamine-induced increase in locomotor activity and increase in extracellular dopamine levels in the nucleus accumbens and striatum of rats. Furthermore, Jones and Holtzman (1992) showed that naloxone is acting centrally to attenuate the locomotor effects of amphetamine, possibly by blocking δ-opioid receptors.

The interaction of opioid receptor antagonists with cocaine, however, is neither as consistent nor as well-defined as the interaction of these drugs with amphetamine. For example, there are conflicting reports on the effects of naltrexone on cocaine-induced behaviors. Naltrexone pretreatment increased (Carroll et al., 1986), decreased (Corrigall and Coen, 1991), and had no effect on cocaine self-administration in rats (Ettenberg et al., 1982). In rhesus monkeys, pretreatment with naltrexone decreased (Mello et al., 1990) and had no effect on (Killian et al., 1978) cocaine self-administration. Furthermore, naltrexone attenuated the acquisition of (De Vry et al., 1989; Ramsey and Van Ree, 1991), but had no effect on the reinstatement of (Comer et al., 1993), cocaine-reinforced responding in rats.

There are similar inconsistencies among studies of interactions between naloxone and cocaine. For instance, there is one report that naloxone reverses the threshold-lowering effects of cocaine in intracranial self-stimulation experiments (Bain and Kornetsky, 1987); however, other studies found no effect of naloxone on the effects of cocaine on intracranial self-stimulation (Van Wolfswinkel et al., 1988; McGregor et al., 1992) or locomotor activity (Jones and Holtzman, 1992).

This study was designed to look further at and compare the interaction of naloxone pretreatment on the behavioral and neurochemical effects of amphetamine and cocaine. The specific objectives were to replicate the findings of Hooks et al. (1992), and to extend these observations to interactions between naloxone and cocaine. In vivo microdialysis was utilized to monitor the change in extracellular concentrations of dopamine in response to cumulative doses of amphetamine or cocaine in awake rats that had been pretreated with naloxone or saline. Dialysate samples were collected from either the nucleus accumbens or striatum, and locomotor activity counts were monitored simultaneously with sample collection.

2. Materials and methods

2.1. Subjects

Male Sprague-Dawley rats (Sasco) weighing between 300–350 g at the time of surgery were used. Between experiments, rats were group housed in a temperature-controlled room on a 12-h light/dark schedule. Rats had free access to food and water.

2.2. Drugs

Naloxone hydrochloride and *d*-amphetamine sulfate (Sigma Chemical Co., St. Louis, MO, USA) were dissolved in 0.9% saline and injected s.c. in a volume of 1.0 ml/kg. Cocaine hydrochloride (Sigma Chemical Co.) was dissolved in 0.9% saline and administered i.p. in a volume of 1.0 ml/kg. Doses of each drug are expressed as the free base.

2.3. Surgery

Rats were anesthetized with 50 mg/kg i.p. sodium pentobarbital (Nembutal; Abbott Laboratories) and placed in a stereotaxic frame with the incisor bar set at +5 mm. A 20 gauge stainless steel guide cannula (Plastics One, Roanoke, VA, USA) was lowered to the dorsal surface of either the nucleus accumbens or striatum. The stereotaxic coordinates for the nucleus accumbens were AP +3.4 and ML ±1.5 from bregma and −6.0 from dura, while those for the striatum were AP +2.5 and ML ±2.7 from bregma and −2.7 from dura (Pellegrino et al., 1979). The guide cannulae were secured with skull screws and cranioplastic cement (Plastics One, Roanoke, VA, USA), and i.m. penicillin (60 000 units) was administered immediately following surgery. Rats were given 3–5 days of recovery before probes were implanted. All surgeries were performed in accordance with the guidelines of the Emory University Institutional Animal Care and Use Committee.

2.4. Apparatus

Locomotor activity counts were measured in Plexiglas photocell cages (40 × 25 × 25 cm) interfaced to an

IBM personal computer. Two horizontal infrared photocell beams were placed 12 cm from the ends of each cage and 2 cm above the floor. Interruption of both beams resulted in a locomotor activity count that was registered by the computer. A 4 inch long fluorescent light on the roof of each cage provided illumination, and white noise was provided to minimize external disturbances.

Microdialysis probes consisted of two lengths of fused silica tubing (40 μm i.d.; 100 μm o.d.; Polymicro Technologies, Phoenix, AZ, USA) inserted into a piece of cellulose dialysis fiber (220 μm o.d.; 6000 MW cutoff; Spectrum Medical Industries, Houston, TX, USA). The ends of the dialysis fiber were sealed with polyimide sealing resin (Alltech). The distance between the silica inlet and outlet lines was 2.0 mm for the nucleus accumbens and 4.0 mm for the striatum. The inlet line of the probe was connected to a 500 μl Hamilton syringe approximately 30 min before probe implantation. Artificial cerebrospinal fluid was contained in the perfusion syringe. Artificial cerebrospinal fluid was composed of 149 mM NaCl, 2.8 mM KCl, 1.2 mM $MgCl_2$, 1.2 mM $CaCl_2$, 0.25 mM ascorbic acid, and 5.4 mM *d*-glucose and was adjusted to a pH of 7.2–7.4 with 0.5 M sodium hydroxide. All chemicals were obtained from Fisher Scientific except L-ascorbic acid, which was obtained from Sigma Chemical Company.

Dialysate samples were analyzed by injecting a 0.5 μl volume of perfusate onto a small-bore high-performance liquid chromatography (HPLC) system. The HPLC system consisted of a 0.5 mm i.d. × 10 cm column (5 μm C-18 stationary phase). Electrochemical detection of dopamine was accomplished using an EG and G Princeton Applied Research amperometric detector using a working electrode (model MF-1000; Bioanalytical Systems (BAS)) with an applied potential of +700 mV versus a Ag/AgCl reference electrode (model RE1; BAS). Dopamine standard solutions were injected onto the HPLC system in order to generate calibration curves.

2.5. Experimental procedure

The evening before the experiment, animals were transferred to the photocell cages and allowed to habituate for 4–5 h. The rats were then weighed and the dialysis probes inserted. The perfusion flow rate of artificial cerebrospinal fluid was initiated at 0.1 μl/min in order to allow dopamine concentrations to equilibrate after the disturbance of probe implantation. Approximately 7 h after probe implantation, the artificial cerebrospinal fluid flow rate was increased to 0.6 μl/min and dialysate samples were collected at 10 min intervals and immediately frozen on dry ice for later analysis. Locomotor activity counts were simultaneously monitored in 10 min bins.

Following the collection of 9 baseline samples, rats were pretreated with a s.c. injection of 5.0 mg/kg naloxone or vehicle. Cumulative doses of s.c. amphetamine (0, 0.1, 0.4, 1.6, 6.4 mg/kg) or i.p. cocaine (0, 3, 10, 30, 56 mg/kg) followed at 30 min intervals. Dialysate samples were collected and locomotor activity monitored for 2 h after the administration of the final dose of drug.

2.6. Histology

Following the experiments, animals were anesthetized with 400 mg/kg chloral hydrate and transcardially perfused with 0.9% saline followed by 10% formalin. The brain was removed and stored in 10% formalin. Probe placement was verified by examining 50 μm coronal sections that were stained with thionine.

2.7. Data analysis

Dialysate dopamine concentrations (expressed as nM dopamine) for each brain region and locomotor activity counts (data pooled from both brain regions) were subjected to a two-factor (pretreatment, time) analysis of variance with repeated measures on time. Separate analyses of variance were performed on the six points from the time of pretreatment to the first dose of drug and on the 21 points from the first dose of drug to the end of the observation period 2 h after the last drug dose. Post-hoc tests were performed where appropriate using a protected Tukey test.

3. Results

3.1. Amphetamine

Nucleus accumbens

The administration of cumulative doses of amphetamine (0.1–6.4 mg/kg) caused a dose-dependent increase in the extracellular levels of dopamine in the nucleus accumbens of both saline- and naloxone-pretreated rats. The highest level of dopamine in the nucleus accumbens was reached 20 min after the administration of the cumulative dose of 6.4 mg/kg amphetamine. While control rats reached an average maximum concentration of 105 ± 13 nM dopamine, naloxone-pretreated rats reached an average maximum concentration of only 64 ± 5 nM dopamine (Fig. 1).

Analysis of variance revealed no significant differences between the pre-amphetamine dialysate dopamine of saline- and naloxone-pretreated rats ($F(1,7) = 0.334$, $P = 0.58$). Analysis of variance did show a signif-

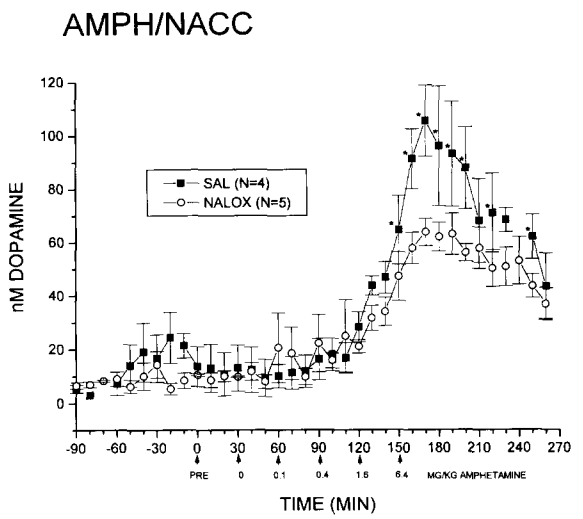

Fig. 1. Naloxone attenuates the amphetamine-induced increase in extracellular dopamine in the nucleus accumbens. After the collection of 9 baseline samples, rats were pretreated with s.c. naloxone (5.0 mg/kg) or saline. Thereafter, at 30 min intervals, a dose of s.c. amphetamine (i.e. 0, 0.1, 0.3, 1.2, 4.8 mg/kg) was administered to give the indicated cumulative dose. Dialysate samples were collected every 10 min until 2 h after the last amphetamine dose was given. Each point represents a mean ± S.E.M. for concentration of dopamine in the dialysate sample. Significant differences between the corresponding points of rats pretreated with naloxone versus saline are indicated by $^{*}P < 0.05$.

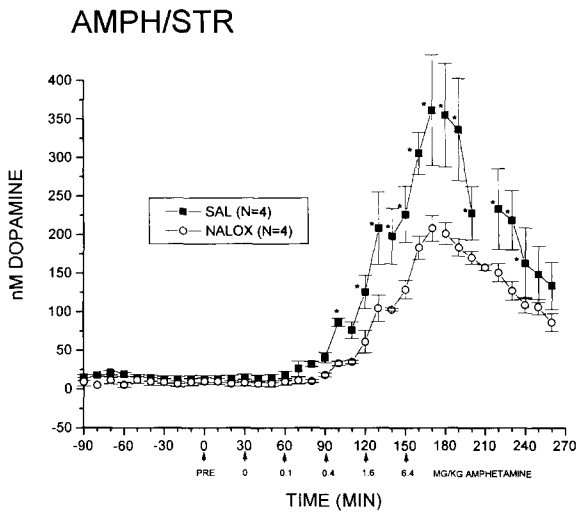

Fig. 2. Naloxone attenuates the amphetamine-induced increase in extracellular dopamine in the striatum. Other details as in Fig. 1.

icant main effect of pretreatment on the post-amphetamine dopamine levels of saline- versus naloxone-pretreated rats ($F(1,7) = 11.0$, $P < 0.01$).

Two hours after the final dose of amphetamine, the average extracellular dopamine levels of saline- and naloxone-pretreated rats declined to approximately the same concentration (saline-pretreated = 43 ± 12 nM dopamine; naloxone-pretreated = 37 ± 6 nM dopamine), but still remained 4 times higher than average baseline concentrations.

Striatum

The administration of cumulative doses of amphetamine (0.1–6.4 mg/kg) caused a dose-dependent increase in the extracellular levels of dopamine in the striatum of both saline- and naloxone-pretreated rats. The highest level of dopamine in the striatum was reached 20 min after the administration of the cumulative dose of 6.4 mg/kg amphetamine. While control rats reached a maximum concentration of 360 ± 72 nM dopamine, naloxone-pretreated rats reached a maximum concentration of only 208 ± 16 nM dopamine (Fig. 2).

Analysis of variance revealed no significant differences between the pre-amphetamine dialysate dopamine levels of saline- and naloxone-pretreated rats ($F(1,6) = 0.916$, $P = 0.37$). Analysis of variance did show a significant main effect of pretreatment on the post-amphetamine dopamine levels of saline- versus naloxone-pretreated rats ($F(1,6) = 12.57$, $P < 0.01$).

Two hours after the final dose of amphetamine, the average extracellular dopamine levels of saline-pretreated rats declined to approximately 134 nM dopamine, while those for naloxone-pretreated rats declined to approximately 86 nM dopamine.

Locomotor activity

Activity data of the subjects for the two dialyzed brain regions were pooled for each pretreatment group (saline and naloxone), and the pooled data were evaluated by analysis of variance (Fig. 3). The administration of cumulative amphetamine doses resulted in a biphasic locomotor activity curve, with the peak in average activity occurring 10 min after the administration of the

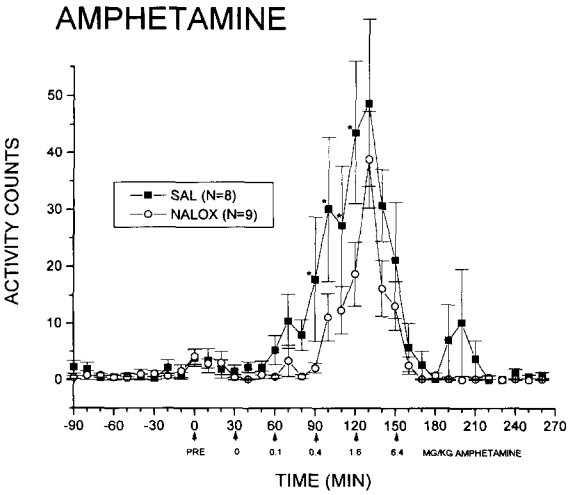

Fig. 3. Naloxone attenuates the amphetamine-induced increase in locomotor activity. Locomotor activity counts were recorded simultaneously with the collection of dialysate samples until 2 h after the last amphetamine dose was given. Other details as in Fig. 1.

1.6 mg/kg cumulative dose. Activity counts then decreased due to an increase in stereotyped behaviors.

Analysis of variance revealed no significant differences among the pre-amphetamine activity levels ($F(1,15) = 0.259$, $P = 0.62$), but did show a significant main effect of pretreatment in the post-amphetamine data ($F(1,15) = 6.744$, $P < 0.05$) for saline versus naloxone. This somewhat marginal interaction is probably due to the tethering of the animals to their probe lines; naloxone produced larger decreases in amphetamine-induced locomotor activity in a variety of studies with untethered animals (e.g., Andrews and Holtzman, 1987; Dettmar et al., 1978; Winslow and Miczek, 1988).

3.2. Cocaine

Nucleus accumbens

The administration of cumulative doses of cocaine (3.0–56 mg/kg) caused a dose-dependent increase in the extracellular levels of dopamine in the nucleus accumbens of both saline- and naloxone-pretreated rats. The highest level of dopamine in the nucleus accumbens was reached 10 min after the administration of the cumulative dose of 56 mg/kg cocaine. While control rats reached an average concentration of 30 ± 5 nM dopamine, naloxone-pretreated rats reached an average concentration of 32 ± 6 nM dopamine (Fig. 4).

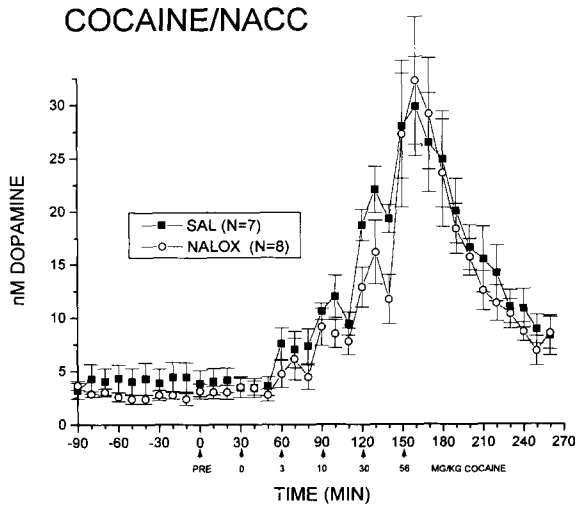

Fig. 4. Naloxone has no effect on the cocaine-induced increase in extracellular dopamine in the nucleus accumbens. After the collection of 9 baseline samples, rats were pretreated with s.c. naloxone (5.0 mg/kg) or saline. Thereafter, at 30 min intervals, a dose of i.p. cocaine (i.e. 0, 3, 10, 30, 56 mg/kg) was administered to give the indicated cumulative dose. Dialysate samples were collected every 10 min until 2 h after the last cocaine dose was given. Each point represents a mean ± S.E.M. for concentration of dopamine in the dialysate sample. Significant differences between the corresponding points of rats pretreated with naloxone versus saline are indicated by $^{*}P < 0.05$.

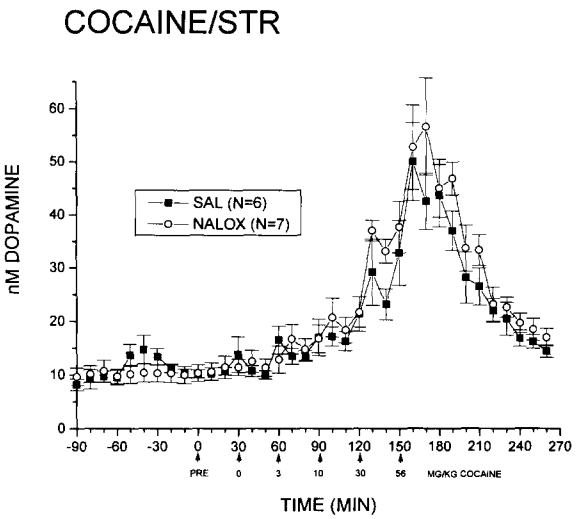

Fig. 5. Naloxone has no effect on the cocaine-induced increase in extracellular dopamine in the striatum. Other details as in Fig. 4.

Analysis of variance revealed no significant main effect of pretreatment between the pre-cocaine ($F(1,13) = 0.339$, $P = 0.57$) or in the post-cocaine dialysate dopamine data ($F(1,13) = 1.24$, $P = 0.29$) of saline- versus naloxone-pretreated rats.

Striatum

The administration of cumulative doses of cocaine (3.0–56 mg/kg) caused a dose-dependent increase in the extracellular levels of dopamine in the striatum of both saline- and naloxone-pretreated rats. For control rats, the highest dialysate dopamine concentration in the striatum was 50 ± 7 nM, 10 min after the administration of the cumulative dose of 56 mg/kg cocaine. Naloxone-pretreated rats obtained the highest dialysate dopamine concentration of 56 ± 9 nM, 20 min after the administration of the cumulative dose of 56 mg/kg cocaine (Fig. 5).

Analysis of variance revealed no significant main effect of pretreatment between the pre-cocaine ($F(1,11) = 0.037$, $P = 0.85$) or between the post-cocaine dialysate dopamine data ($F(1,11) = 2.282$, $P = 0.16$) of saline- versus naloxone-pretreated rats.

Locomotor activity

Activity data of the subjects for the two dialyzed brain regions were pooled for each pretreatment group (saline and naloxone), and the pooled data were evaluated by analysis of variance (Fig. 6). The administration of cumulative doses of cocaine resulted in a biphasic locomotor activity curve, with the peak in average activity occurring 10 min after the administration of the 56 mg/kg cumulative dose. Activity counts then decreased due to an increase in stereotyped behaviors.

Analysis of variance revealed no significant main effect of pretreatment among the six pre-cocaine

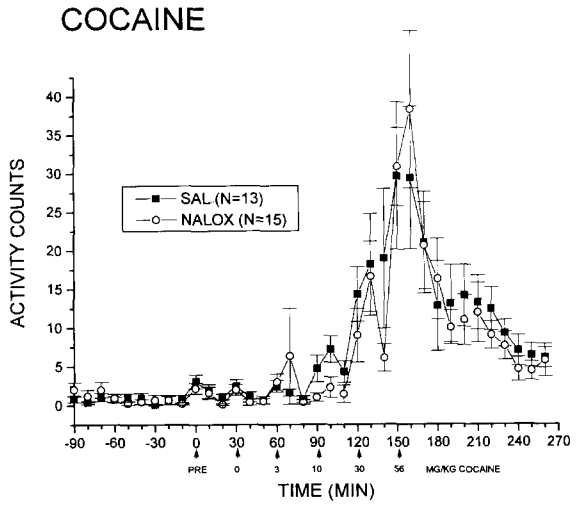

Fig. 6. Naloxone has no effect on the cocaine-induced increase in locomotor activity. Locomotor activity counts were recorded simultaneously with the collection of dialysate samples until 2 h after the last cocaine dose was given. Other details as in Fig. 4.

($F(1,26) = 1.205$, $P = 0.28$) or in the post-cocaine activity points ($F(1,26) = 0.227$, $P = 0.64$) for saline versus naloxone.

4. Discussion

The results of this study confirm previous findings that pretreatment with naloxone attenuates both the neurochemical and locomotor activity effects of amphetamine (Hooks et al., 1992; Holtzman, 1974). In rats treated with cumulative doses of amphetamine, naloxone reduced the maximum dopamine concentration reached in both the nucleus accumbens and striatum by approximately 40% compared to animals pretreated with saline. In contrast, naloxone pretreatment had no significant effect on the increase in extracellular dopamine in either the nucleus accumbens or striatum of rats treated with cumulative doses of cocaine. Furthermore, in agreement with the results of Jones and Holtzman (1992), naloxone pretreatment had no effect on the cocaine-induced increase in locomotor activity.

The reason that naloxone attenuates the neurochemical and behavioral responses of amphetamine but not those of cocaine is not clear. This differential interaction may stem from the fact that each drug increases extracellular dopamine by a different mechanism. While the main action of cocaine is to block the reuptake of dopamine into presynaptic terminals (Heikkila et al., 1975), the main action of amphetamine is to cause the release of dopamine from presynaptic terminals (Arnold et al., 1977; Dayton et al., 1979; Fischer and Cho, 1979). It is possible, then, that naloxone has a direct action on the presynaptic terminal, such as an interaction with the dopamine transporter. By this mechanism, naloxone may inhibit the neuronal uptake of dopamine and/or block amphetamine-induced dopamine release or synthesis, actions that would have no effect on the cocaine-induced increase in extracellular dopamine. However, there does not appear to be any suggestion in the literature that naloxone has any such presynaptic actions. Moreover, naloxone did not alter basal levels of dopamine, which would tend to rule out the inhibition of dopamine uptake by naloxone.

Amphetamine, but not cocaine, is known to release directly several different neurotransmitters. Amphetamine, therefore, may also promote the release of endogenous opioids, either directly, or as an indirect consequence of the release of one of the other neurotransmitters. Opioids have been shown to increase the firing of ventral tegmental dopamine neurons (Nowycky et al., 1978; Matthews and German, 1984) and to increase dopamine release and turnover in the nucleus accumbens (Philips and Fibiger, 1978; Smith and Lane, 1983; Di Chiara and Imperato, 1988b). Opioids have also been shown to inhibit the firing of non-dopamine neurons in the ventral tegmental area (Gysling and Wang, 1983), many of which are proposed to contain γ-aminobutyric acid (GABA). Furthermore, Klitenick et al. (1992) showed that morphine administered via a microdialysis probe directly into the ventral tegmental area increased extracellular dopamine concentrations and decreased extracellular GABA concentrations. This effect can be blocked by systemically administered naloxone. Electrophysiological studies have demonstrated that non-dopamine neurons in the substantia nigra and ventral tegmental area are hyperpolarized by the application of μ-opioid receptor agonists, but that dopamine neurons are unaffected (Lacey et al., 1989; Johnson and North, 1992). Furthermore, autoradiographic studies indicate a localization of μ- and δ-opioid receptors on non-dopaminergic, but not on dopaminergic, neurons in the ventral tegmental area (Dilts and Kalivas, 1989). Taken together, this evidence supports the hypothesis that the excitatory effect of opioids on dopamine neurons may occur via an indirect mechanism, i.e. the removal of a tonic inhibitory GABA input on the dopamine neuron (Johnson and North, 1992; Klitenick et al., 1992; Ronken et al., 1993). Therefore, the increase in extracellular dopamine seen after treatment with amphetamine may be due partly to the releasing action of amphetamine directly on dopamine neurons and partly due to an amphetamine-induced release of endogenous opioids. The opioids, in turn, increase dopamine levels even further by hyperpolarizing local inhibitory GABAergic interneurons, thereby causing the disinhibition of dopamine neurons. Pretreatment with naloxone would block the ability of endogenous opioids to hyperpolarize GABAergic interneurons and, therefore, leave the inhibitory influ-

ence on the dopaminergic neurons intact. This would result in an attenuation of the amphetamine-induced increase in extracellular dopamine. In contrast, if the mechanism of action of cocaine does not involve opioidergic neurotransmission, the neurochemical and behavioral effects of cocaine would not be affected by naloxone pretreatment.

Another possible explanation for our results is that there is a pharmacokinetic interaction between naloxone and amphetamine. For example, naloxone might increase the rate of metabolism of amphetamine or otherwise reduce the concentration of amphetamine in the brain. We did not measure tissue levels of amphetamine in this study. However, a pharmacokinetic basis for the selective interaction of naloxone with amphetamine versus cocaine is unlikely since comparable behavioral effects have been seen with centrally administered naloxone methiodide (Jones and Holtzman, 1992). Furthermore, results similar to those obtained in this study with systemically administered naloxone also are produced by central administration of the specific δ-opioid receptor antagonist naltrindole. Naltrindole reduced the increases in locomotor activity (Jones et al., 1993) and extracellular striatal dopamine (Schad et al., in preparation) produced by amphetamine but not those produced by cocaine. Therefore, it is most likely that naloxone is modifying the effects of amphetamine by acting at opioid receptors to block the actions of endogenous opioids.

In conclusion, these data replicate previous findings that pretreatment with naloxone attenuates the neurochemical and behavioral effects of amphetamine. In addition, these data extend the observations to the interactions between naloxone and cocaine. Unlike amphetamine, naloxone was shown to have no effect on either the neurochemical or behavioral effects of cocaine. These results indicate that endogenous opioids play a role in mediating the neurochemical and behavioral responses to amphetamine but not to those of cocaine.

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